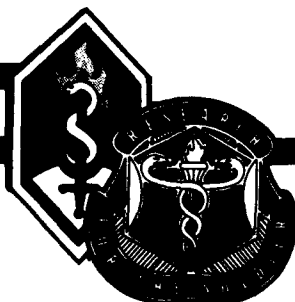


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**The Effects of Pyridostigmine Bromide
on Visual Performance
(Reprint)**

By

**Roger W. Wiley
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Sensory Research Division



May 1993

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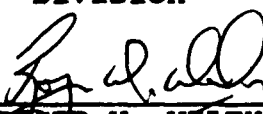
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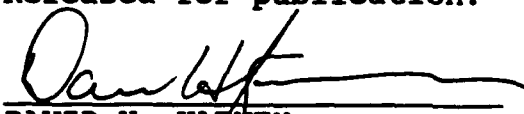
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The Effects of Pyridostigmine Bromide on Visual Performance

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WILEY RW, KOTULAK JC, BEHAR I. *The effects of pyridostigmine bromide on visual performance*. *Aviat. Space Environ. Med.* 1992; 63:1054-9.

The effects of pyridostigmine bromide (PB) on selected visual functions were measured on four healthy aviator candidates. Following a pretreatment day during which baseline measurements were completed, subjects were administered currently recommended doses (30 mg, t.i.d.) of PB for 3 d during which their visual functions were assessed using a repeated measures design. Spatial resolution ability was evaluated with high and low contrast visual acuity charts and contrast sensitivity charts at three luminance levels. Dark adaptation was evaluated by measuring visual thresholds for 40 min after a standardized retinal photopigment bleach. Also, refractive error and several oculomotor functions (lateral phoria, fusional vergence, accommodative amplitude, and pupil size) were measured. On days that the subjects ingested PB, only refractive error and pupil diameter were significantly different, and these only minimally. We conclude that the use of PB at doctrinal doses will not significantly compromise an aviator's visual ability.

PYRIDOSTIGMINE BROMIDE (PB), a quaternary carbamate which is used as a pretreatment drug against potential nerve agent exposure, reversibly binds acetylcholinesterase, thereby preventing the hydrolysis of the neurotransmitter acetylcholine at neural synapses (20). Therefore, possible side effects (20) for individuals taking PB are related to stimulation of those physiological systems mediated by the cholinergic system. Muscarinic side effects include gastrointestinal upset, bradycardia, increased salivation and bronchial secretions, diaphoresis, and miosis. Nicotinic side effects are muscular fasciculations and weakness.

Recent reports have provided insight about the potential impact on military operations of side effects associated with ingestion of PB. For example, several studies have investigated the physiological response to heat and exercise with PB-dosed volunteers. Various

biochemical assays indicate that the physiological effects from PB with moderate temperature and exercise are minimal (21). However, PB apparently reduces skin blood flow and may adversely affect thermoregulation in more severe environments (16). None of the subjects experienced significant symptoms during the present study, although two of the four subjects commented that they thought that were slightly more fatigued. They all continued to maintain active exercise programs.

Other studies have been directed toward the special demands that might arise from aviators taking PB. Boll et al. (3) did not find any changes in +G_z tolerance or hand grip strength among subjects after ingesting PB. Dellinger et al. (7) monitored heart rate and vagal tone in C-130 aircrew flying simulated missions after taking PB or a placebo. While there were no drug effects in basic heart rate or vagal tone, during the simulated drop segments of the mission, heart rate increased and vagal tone decreased significantly among aircrew having the placebo. In a study by Gawron et al. (10), C-130 pilots flew simulated missions after taking either PB or a placebo. The results indicated that PB did not hinder successful mission completion or cause a greater number of navigation or airdrop errors. In comparison, Harriman et al. (12) investigated the effects of PB on A-10 pilots. These pilots took either PB or a placebo prior to executing a variety of mission profiles. On flight days when PB was given, 50% of the pilots reported 27 subjective symptoms compared to placebo days in which only 21% of the pilots presented with 6 symptoms. Also the PB apparently caused decreased heart rates and increased skin temperatures. These studies have shown that, although PB causes some subjective symptoms, the physiological changes are relatively minor and apparently do not compromise flying ability.

The underlying logic for selecting a quaternary compound such as PB as a pre-exposure therapy, rather than a tertiary carbamate such as physostigmine salicylate, equally effective in binding acetylcholinesterase, is that PB presumably does not cross the blood-brain barrier. Therefore, there should be an absence of central effects caused by the drug. It is reasonable to

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assume that sensory systems, such as vision, would remain unaffected. Indeed, several neurophysiological investigations have demonstrated central visual system changes following administration of physostigmine salicylate which do not occur with currently recommended (doctrinal) dose levels of PB (i.e., 30 mg, t.i.d.), even when the blood cholinesterase inhibition has been achieved (6,15). Additional evidence for the absence of a central neural response following PB is provided by several visual psychophysical experiments. Graham and Cook (11) did not demonstrate any significant changes in static visual acuity, stereopsis, or contrast sensitivity among a large number of subjects taking PB. Similarly, Borland et al. (4) found that PB did not influence static visual acuity while their subjects' performance improved in a dynamic acuity task with PB. Kay and Morrison (14) reported a small but significant improvement in contrast sensitivity as well following ingestion of PB. These latter investigators repeated their experiments using a technique which eliminated optical effects, and, under these viewing conditions, the improvement in contrast sensitivity was not present.

The present investigation was initiated to determine if changes in parasympathetic activity caused by PB ingestion were sufficient to degrade visual performance, particularly at low light levels. Potential changes in the ocular components which contribute to image formation were of special interest. Also, since previous studies (4,11) have reported difficulties in oculomotor tracking with PB, clinical measurements to assess oculomotor function were included.

MATERIALS AND METHODS

Subjects

Four male subjects (average age = 23 years) who were awaiting initial flight training volunteered for the study. All subjects had completed intensive flight medical examinations and were considered to be in good health.

The subjects were admitted to a military hospital during the period of the study and the PB was administered by nursing personnel. This was to insure that the PB (30 mg, t.i.d.) was ingested on schedule and to control nutritional intake.

Study Procedures

Five test sessions on consecutive days, each requiring approximately 3 h, were completed for all subjects. The first day was pre-drug to establish baseline scores. Days 2, 3, and 4 were PB days, and day 5 was the post-drug day to insure no residual effects from PB remained. Published pharmacokinetic parameters indicate that the elimination half-life of PB is approximately 1.8 h and its bioavailability is 7.6 h (1).

The subjects were divided into pairs and reported to the research laboratory for testing either in the morning or afternoon sessions. Following clinical and psychophysical testing, blood samples were obtained and analyzed, using the technique of Ellman et al. (8), to determine blood cholinesterase levels so that inhibition levels could be inferred.

Spatial Vision

Spatial vision was evaluated using two chart tests, one of which provided an estimate of contrast sensitivity (CS), while the other test determined high and low contrast visual acuity (VA). The charts were evenly illuminated by two banks of stand-mounted fluorescent lamps that provided a chart background luminance of approximately 88.5 cd/m². Binocular thresholds were obtained at three luminance levels, adjusted by viewing the charts either with no filters or with neutral density filters of optical density (OD) 2 or 4 (light transmission of 1% or 0.01%, respectively) in front of the eyes. Therefore, the effective chart luminance was 88.5 cd/m², 0.885 cd/m², or 0.0089 cd/m². As the subjects were dark adapted at the start of spatial vision testing, they were first tested using the 4-OD filters, then the 2-OD filters, and finally with unobstructed viewing. The order of testing at each luminance level was as follows: CS, high contrast VA, then low contrast VA. Practice effects within a given day were minimized by using two equivalent versions of each chart, one with the 4-OD filters and with no filter, while the other was used with the 2-OD filters.

The Pelli-Robson chart was used to obtain an estimate of CS. This chart consists of eight lines of six letters. All letters are the same size, subtending 0.5° visual angle at the viewing distance of 3 m. This letter size is assumed to provide an estimate of contrast sensitivity equivalent to that obtained using sinusoidal gratings of a spatial frequency between 3 and 5 cycles/° (19). There are two groups of three letters each on each line of the chart. The letters in each group have the same contrast and the log contrast for each successive group is reduced by 0.15. The highest contrast letters are at the top of the chart with lower lines having reduced contrast in an orderly fashion.

Visual acuity was measured with the Bailey-Lovie high and low contrast visual acuity charts (2). These charts consist of 14 rows of 5 letters. Letters on the high contrast chart appear black against the white background and have a nominal contrast of 90%, while letters on the low contrast chart appear light gray and have a nominal contrast of 8%. Subjects were tested at 4.6 m. At this testing distance, the largest letters have a VA requirement of 20/166.4 (logMAR 0.92) and the smallest letters have a VA demand of 20/8.3 (logMAR -0.38).

Oculomotor Functions

The effects of PB on the eye's muscle systems were assessed by evaluating five representative oculomotor functions. Three of these functions are known to be affected by parasympathomimetic drugs which PB also might mimic; namely, pupil diameter (18), amplitude of accommodation (9), and refractive error (9); the latter because of ciliary spasm causing excessive accommodation. In addition, previous investigations suggest that the lateral phorias might be affected indirectly through alteration of the relationship between accommodative vergence and accommodation (5,9). The fifth function chosen for study, fusional vergence, has not been shown to be influenced by parasympathomimetics.

A phoria can be simply defined as a deviation of the lines of sight when fusion is prevented. A deviation towards the nasal midline is referred to as an esophoria, whereas one away from the midline is termed an exophoria. In the present study, the phorias were measured using the von Graefe method in which a variable-power prism was placed with a vertical axis orientation before the left eye to disrupt fusion and a horizontal prism was used before the right eye to align the two vertically-separated images. The amount of horizontal prism required to achieve alignment is the magnitude of the phoria, and the direction of the prism base (i.e., exophoria, base in; esophoria, base out) determines its direction.

Fusional vergence, the oculomotor system's compensatory mechanism for a phoria, was measured with the Risley prisms oriented with their bases either in or out in front of both eyes while the subjects viewed a target at either 6 m or 40 cm. The amplitude of fusional convergence or divergence was taken to be the greatest amount of base out or base in prism, respectively, that could be tolerated before the subjects reported either blur or diplopia.

Pupil diameter was measured using a millimeter rule while the subjects were completely adapted to either room illumination (25 fc) or in a darkened room. The subjects were instructed to look straight ahead at a distant object to obviate pupil effects associated with accommodation and convergence. For the darkened room measurements, the investigator wore night vision goggles and used infrared illumination to determine the pupil diameters.

The amplitude of accommodation defines the limit of the operation range of the focusing system of the eye. For this experiment, the device used to assess this function was the Prince's Rule which consists of a threshold-sized visual stimulus on a card attached to and moved along a calibrated shaft. The amplitude of accommodation is taken to be the reciprocal of the nearest distance from the eye that the target can be seen clearly. Although used commonly in eye clinics, the Prince's rule actually does not measure accommodative response, but it does specify the stimulus to accommodation that elicits the maximal response. Under the conditions of this experiment (photopic luminance, high contrast target), the accommodative stimulus tends to be similar to the accommodative response (13,17).

While refractive error is not an oculomotor function per se, transitory changes in refraction under the influence of parasympathomimetics have been attributed to alternations in tonic accommodation; i.e., ciliary spasm (9). The refractive errors of our subjects were assessed objectively using a commercial autorefractor (Nidek Autorefractor/Keratometer, Model ARK-2000). This device measures both the spherical and cylindrical (astigmatic) components of the refractive error. To assist

in the analysis, the spherocylindrical refractive error was converted to an equivalent sphere value (one half the cylinder added to the sphere component).

Dark Adaptation

Dark adaptation was measured with a clinical Goldmann/Weekers Adaptometer. An identical test procedure was used for all subjects on each of the five test days. At the start of each test session, the subject was seated in a dimly illuminated room (5 fc) for 5 min. Following this period, all lights were turned off and the subject remained in the dark for 3 min. During this time, his left eye was occluded and he positioned himself comfortably in front of the hemispherical Ganzfeld of the adaptometer. Following this period, the hemisphere was illuminated and the subject was light adapted by staring into the uniformly bright (321 fL) Ganzfeld. After the 5-min period of light adaptation, the hemisphere lighting was extinguished and the fixation light became visible. Light threshold measurements started immediately.

An ascending method of limits was used with the subject indicating when the test stimulus became visible by tapping on the instrument table. The angular subtense of the test stimulus was 10° and it stimulated a portion of retina approximately 10° below the fovea. Threshold measurements were made every minute for 40 min after the light adaptation period.

RESULTS

Mean contrast sensitivity thresholds (expressed in log contrast sensitivity) for the four subjects are given in Table I, where it may be seen that CS is very strongly affected by luminance condition, but did not differ from day to day over drug conditions. The luminance effect is statistically significant ($F_{2/6} = 3180.3$, $p < 0.0001$), while neither the day's effect nor the luminance-by-days interaction is significant. The comparison of days 1 and 5 (no drug) vs. days 2-4 (drug) also is not significant.

Mean visual acuity thresholds (expressed in logMAR values) for the four subjects for each of the 5 d of the study are given in Tables II and III for high and low contrast VA, respectively. For these tables, the data were retained in logMAR units to calculate their means which were then converted to Snellen equivalents for display.

As was found for CS, high contrast VA thresholds were also strongly affected by luminance variation, but did not differ from day to day over drug conditions. The luminance effect is statistically significant ($F_{2/6} = 1211.2$, $p < 0.0001$), while neither the day's effect nor the luminance-by-days interaction is significant. The comparison of days 1 and 5 (no drug) vs. days 2-4 (drug) again is not significant.

TABLE I. LOG CONTRAST SENSITIVITY FOR DIFFERENT LUMINANCE LEVELS FOR EACH TEST DAY.

Luminance	Pre	T-day 1	T-day 2	T-day 3	Post
Filter 4 OD	0.39	0.39	0.42	0.53	0.49
Filter 2 OD	1.62	1.62	1.66	1.66	1.66
No filter	1.92	1.85	1.88	1.92	1.96

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TABLE II. LogMAR (AND SNELLEN) HIGH CONTRAST VISUAL ACUITY WITH THE DIFFERENT LUMINANCE LEVELS FOR EACH TEST DAY.

Luminance	Pre	T-day 1	T-day 2	T-day 3	Post
Filter 4 OD	0.76 (20/115)	0.76 (20/115)	0.79 (20/123)	0.72 (20/105)	0.75 (20/112)
Filter 2 OD	0.07 (20/23)	0.07 (20/23)	0.07 (20/23)	0.05 (20/22)	0.02 (20/21)
No filter	-0.16 (20/14)	-0.13 (20/15)	-0.12 (20/15)	-0.17 (20/14)	-0.20 (20/13)

TABLE III. LogMAR (AND SNELLEN) LOW CONTRAST VISUAL ACUITY WITH THE DIFFERENT LUMINANCE CONDITIONS FOR EACH TEST DAY.

Luminance	Pre	T-day 1	T-day 2	T-day 3	Post
Filter 4 OD	>0.92 (>20/116)	>0.92 (>20/116)	>0.92 (>20/116)	>0.92 (>20/116)	>0.92 (>20/116)
Filter 2 OD	0.33 (20/43)	0.38 (20/48)	0.38 (20/48)	0.36 (20/46)	0.33 (20/43)
No filter	0.10 (20/25)	0.08 (20/24)	0.08 (20/24)	0.06 (20/23)	0.06 (20/23)

The results for low contrast VA parallel those found for CS and for high contrast VA. Thresholds again were strongly affected by luminance variation, but did not differ from day to day over drug conditions. When the 4 OD filters were used, not even the largest letters on the low contrast VA chart were visible to any subject, and this condition was eliminated from further analysis. The luminance effect for the remaining two levels is statistically significant ($F_{1/3} = 85.1$, $p < 0.0027$), while neither the day's effect nor the luminance-by-days interaction is significant. As with the previous analyses, the comparison of data from days 1 and 5 (no drug) vs. days 2-4 (drug) is not significant.

Analyses of variance with repeated measures were used to examine the oculomotor data. If at least one of the means was found to differ statistically from the remainder, a "contrast over a within factor" analysis was done to determine if the difference might be an effect of pyridostigmine; i.e., results from drug vs. non-drug test days were compared.

Of the six tests assessing oculomotor function, four were not affected by PB. The phorias (Fig. 1) showed no statistically significant effect with test distance or with

PB (experimental test day). Fusional divergence (Fig. 2), however, did show an effect for test distance (6 m vs. 40 cm). However, since this test distance effect could not be related to PB, it was not analyzed further. There was no significant difference for test day. The fusional convergence results (Fig. 3) did not vary significantly with test distance or test day. Fig. 4 shows the data from the amplitude of accommodation measurements. Again, there were no statistically significant effects of the PB test days vs. non-drug days.

The remaining clinical visual tests, pupil diameter and refractive error, both demonstrated significant results which might be related to PB. The pupil diameter measurements (Fig. 5) were significantly affected by light level, an expected finding and most probably not associated with the PB. However, the pupil diameters were significantly different ($p < 0.02$) on non-drug days (pre and post) and drug days (T-1, T-2, and T-3). Finally, refractive error (accommodative spasm) (Fig. 6) showed a significant effect and a contrast over a within factor analysis revealed a significant difference ($p < 0.02$) between non-drug and drug day measurements.

The data for recovery of visual sensitivity following

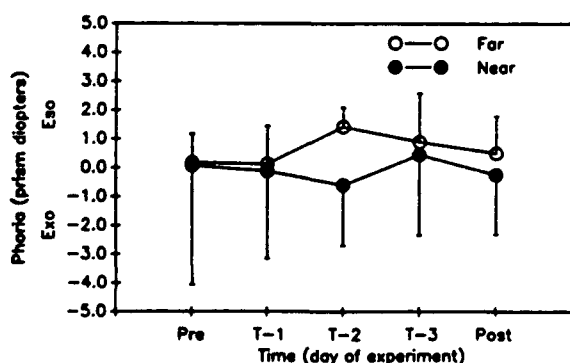


Fig. 1. Lateral phoria measurements (prism diopters) at 6 m (far) and 40 cm (near) for each test day. Average of 4 subjects.

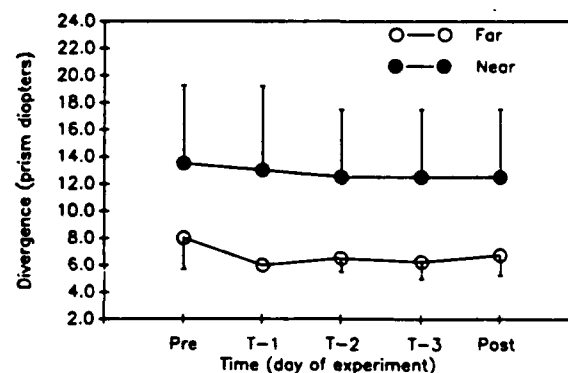


Fig. 2. Fusional divergence (prism diopters) at 6 m and 40 cm for each test day. Average of 4 subjects.

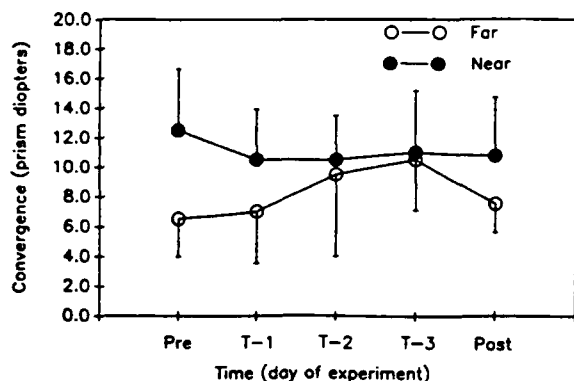


Fig. 3. Fusional convergence (prism diopters) at 6 m and 40 cm for each test day. Average of 4 subjects.

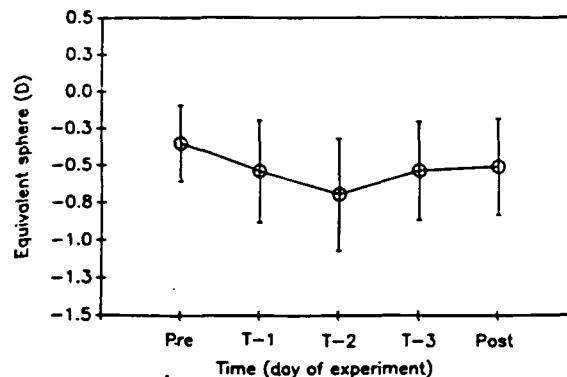


Fig. 6. Average refractive error (equivalent sphere) measured on each test day.

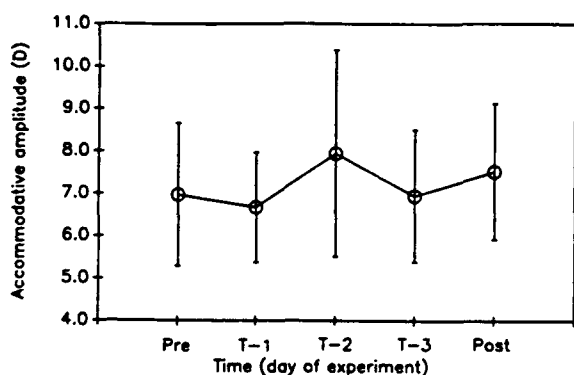


Fig. 4. Maximum accommodative response (diopters) for each test day. Average of 4 subjects.

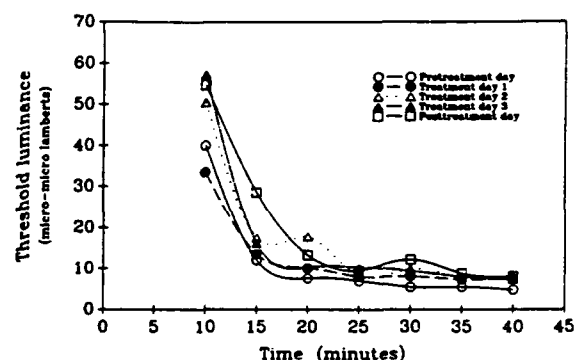


Fig. 7. Average threshold luminance over time following retinal photopigment bleaching with white light.

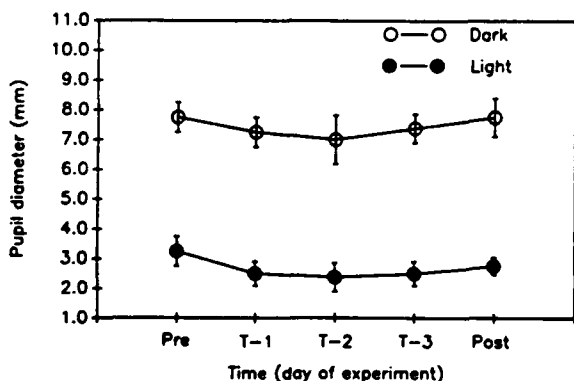


Fig. 5. Average pupil diameter when the subjects are seated in a lighted room (25 fc) or in complete darkness.

retinal bleaching are shown in Fig. 7. For this figure, the average visual threshold from the four subjects is plotted for the various times between 10 and 40 min following exposure to the bleaching light. As can be seen, except for minor perturbations, the curves are practically superimposed with the average thresholds obtained on the two non-drug days providing the maximum and minimum values for most of the postexposure

times. Because our subjects demonstrated a wide variation in the PB effect reflected by blood cholinesterase inhibition, the absolute visual thresholds for every subject on each test session were plotted as a function of % AChE inhibition for that test day. These data are shown in Fig. 8. While there is a minor positive relationship, indicating a slight increase in threshold with increasing inhibition, the variation in threshold values is quite large. This is suggested by the small coefficient of determination (r^2) value.

DISCUSSION

Our results indicate that ingestion of pyridostigmine bromide at military doctrinal levels for pre-exposure therapy against potential nerve agents should not compromise visual performance. Although data were obtained for these levels from only four subjects, the changes observed were quite minimal. For example, low contrast acuity with dim illumination (Table III) is a very demanding task and should reveal even subtle effects. Our subjects did not demonstrate any significant changes in their spatial vision performance with this difficult task although, for the dimmest lighting condition, they could not see the largest low contrast target regardless of drug vs. non-drug day.

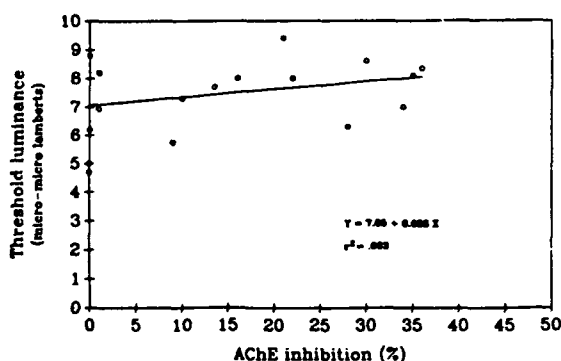


Fig. 8. Absolute light sensitivity as a function of measured blood acetylcholinesterase inhibition. Several of the data pairs had identical values so their corresponding data points are superimposed in the figure.

Among the extensive oculomotor testing, only two functions were found to be significantly affected by PB. Our subjects were slightly more myopic (0.25–0.50 diopters) for those test days on which they had PB (Fig. 6). Also, their pupil diameters were slightly, but significantly, smaller on those same test days (Fig. 5). Both of these results probably can be attributed to increased parasympathetic activity secondary to cholinesterase inhibition. Increased parasympathetic activity would stimulate the pupillary sphincter to reduce pupil diameter and could cause a minor ciliary spasm with a consequent slight myopic shift. For distance vision, these results would be in counterbalance as demonstrated by the unchanged spatial vision results. Normally, an increase in myopia should be accompanied by a corresponding decrease in distance acuity. However, a smaller pupil diameter would increase the depth of focus and serve to reduce refractive error effects. This is especially true for those results obtained under brighter conditions. As mentioned previously, Kay and Morrison (14) reported a slight improvement in contrast sensitivity when their subjects were influenced by PB. No improvement was seen when they eliminated optical and pupillary aperture effects. Another possible secondary effect from a smaller pupil is a reduction in the amount of light reaching the retina. However, the results shown in Fig. 7 and 8 which display changes in visual sensitivity over time and with different cholinesterase inhibition levels suggest that this reduction is negligible.

These data were obtained in a relatively quiet, controlled laboratory milieu, free from competing demands for attention, decisions, and responses as found in a hot, noisy, and dusty cockpit. However, the few changes in visual performance we found were minimal and should not significantly change with the added stressors encountered during flight. We conclude that ingestion of pyridostigmine bromide will not adversely affect an aviator's visual ability. However, it should be noted that our data were obtained from subjects ingesting PB for only 3 d and the highest blood cholinesterase inhibition achieved was 35%. While not expected, the visual effects could be different with higher inhibition levels or longer ingestion periods.

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